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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/935,061	08/21/2001	Brian K. Kobilka	STAN-213	7757

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EXAMINER	
LI, RUIXIANG	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 04/19/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/935,061	KOBILKA ET AL.	
	Examiner	Art Unit	
	Ruixiang Li	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 April 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *20-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *20-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments, and/or Claims

On further consideration, the finality of the rejection of the last Office action is withdrawn.

Applicants' amendment filed on 04/03/2006 has been entered in full. Claims 1-13 have been canceled. Claims 20-24 are pending and under consideration.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Withdrawn Objections and/or Rejections

The rejection of claims 1-4 and 9-12 under 35 U.S.C. 103(a) as being unpatentable over Dunham et al. (J. Biol. Chem. 274:1683-1690, 1999) in view of Gether et al. (The EMBO Journal 16:6737-6747, 1997) have been withdrawn in view of canceled claims.

The rejection of claims 1, 5-7, and 13 under 35 U.S.C. 103(a) as being unpatentable over Farrens et al. (*Science* 274:768-770, 1996) in view of Parola et al. (*Analytical Biochemistry* 254, 88-95 91997) have been withdrawn in view of canceled claims.

The objection to claim 8 has been withdrawn in view of canceled claim.

Claims Rejections under 35 U.S.C. 103(a)

(i). Claims 20-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dunham et al. (J. Biol. Chem. 274:1683-1690, 1999) in view of Gether et al. (The EMBO Journal 16:6737-6747, 1997).

Dunham et al. teach conformational changes in rhodopsin upon photoactivation using a series of rhodopsin mutants containing single reactive cysteine residues in the cytoplasmic side of helix F (3rd intracellular loop)(see Fig. 1; abstract; the middle of right column of page 1685), including the mutant V250C; such a conformational change exposes the cytoplasmic loops and allows transducin to bind and become activated (2nd paragraph of right column of page 1683). The cysteine mutants were studied in two ways, by measuring their reactivity to a cysteine-specific reagent (PyMPO-maleimide) and by labelling the cysteins with a fluorescence label (monobromobimane) followed by fluorescence spectroscopic analysis (Abstract). Since the fluorescence change was measured in a 4-mm black jacketed cuvette containing 0.08% DβM (a detergent; left column of page 1685), the rhodopsin receptor would be in a membrane of detergent micelles (see page 13 of the instant specification for definition) and attached to cuvette (a immobilization phase), via either the N-terminal portion or C-terminal portion. Dunham et al. also teach that the rhodopsin antagonist, 11-cis-retinal, is covalently bound in the middle of helices, inactivating the protein in the dark state. Light causes the isomerization of 11-cis retinal to the all-trans form and activates the receptor (page 1683). Dunham et al. further teach reactivity measurement of rhodopsin cysteine mutants with PyMPO-maleimide using sample wells (the 2nd and 3rd paragraphs of right

column of page 1684, in particular, last line of the 3rd paragraph of page 1684; bottom of right column of page 1685; Fig. 3 and Fig. 4C), which are necessarily arranged in a specific order, i.e., an array.

Dunham et al. fail to explicitly teach a method of identifying a ligand of a G protein coupled receptor (GPCR), for example, for a hormone or neurotransmitter, by detecting a conformationally sensitive fluorescent probe located within the third intracellular domain of the GPCR.

Gether et al. teach a human β2 adrenergic receptor, a member of the superfamily of hormone and neurotransmitter GPCR, has 13 Cys residues one of which is located within the third intracellular loop (Fig. 1).

Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to apply the method of Dunham et al. to a human β2 adrenergic receptor to use PyMPO-maleimide, a cysteine-specific reagent, as a conformationally sensitive probe to detect the conformational change of a human β2 adrenergic receptor and thus to identify a ligand of the human β2 adrenergic receptor with a reasonable expectation of success. PyMPO necessarily labels cysteine 265, which is located within the third intracellular domain, without labeling the cysteines in the transmembrane domains due to the large size of the PyMPO molecule (Fig. 2 of Dunham et al.). One would have been motivated to do so because Dunham et al. teach that the

conformational change described in the study is a conserved ad primary step in the activation of GPCRs, such as β-adrenergic receptor (right column of page 1689), and that the approaches used in the study should be applied to measurement of conformational changes of other GPCRs (top of page 1690).

(ii). Claims 1 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Farrens et al. (*Science* 274:768-770, 1996) in view of Parola et al. (*Analytical Biochemistry* 254, 88-95 91997).

Farrens et al. teach detecting photoactivated conformational changes in rhodopsin using spin-labelled double cystein mutants. Each contains one cysteine at the cytoplasmic end of helix C (Cys^{139}) and one cysteine at various positions in the cytoplasmic end of helix F (see Abstract; Fig. 1). Farrens et al. also teach that rhodopsin has a site of V-8 proteolysis that is located within the conformationally sensitive third intracellular domain (see, e.g., Fig. 1). After V-8 digestion, rhodopsin was cleaved primarily into two large fragments: an N-terminal fragment (~27 kD) and a C-terminal fragment (~13 kD) on SDS-PAGE (Figs. 1 and 3). The various rhodopsin mutants for V-8 proteolysis (see, e.g., Fig. 3) are necessarily arranged in a specific order, i.e., an array.

Farrens et al. fails to teach a method of identifying a ligand of a G protein coupled receptor (GPCR), for example, for a hormone or neurotransmitter by detecting a

conformationally sensitive protease cleavage product resulted from a cleavage site within the third intracellular domain of the GPCR.

Parola et al. teach a human β2 adrenergic receptor, a member of the superfamily of hormone and neurotransmitter GPCR, has a site within the third intracellular loop, which can be cut by protease factor Xa (Fig. 1). After protease factor Xa digestion, the human β2 adrenergic receptor was cleaved into two large fragments: an N-terminal fragment and a C-terminal fragment on SDS-PAGE (Fig. 5).

Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to apply the method of Farrens et al. to a human β2 adrenergic receptor to use protease factor Xa proteolysis, as a conformationally sensitive probe to detect conformational change of a human β2 adrenergic receptor and thus to identify a ligand of the human β2 adrenergic receptor with a reasonable expectation of success. One would have been motivated to do so because human β2 adrenergic receptor shares both homology in primary amino acid sequence and similarity in topology with rhodopsin as taught by Parola et al. (top of right column of page 88) and the conformational changes upon activation are conserved in all GPCRs that mediates the actions of extracellular signals of light, odorants, hormones, and neurotransmitters (see, top of page 768 and the end of the article of Farrens et al).

Conclusion

No claims are allowable.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ruixiang Li whose telephone number is (571) 272-0875. The examiner can normally be reached on Monday through Friday from 8:30 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback, can be reached on (571) 272-0961.

Communications via Internet e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to [Brenda.Brumback@uspto.gov]. All Internet e-mail communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists a possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of 35 U.S.C. 122. This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark on February 25, 1997 at 1195 OG 89.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

RUIXIANG LI, PH.D.
PRIMARY EXAMINER

Ruixiang L.

Ruixiang Li, Ph.D.
Primary Examiner
April 15, 2006